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Health and Environmental Effects Profile for 2-Methyl-5-Nitroaniline

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16. ABSTRACT

The Health and Environmental Effects Profile for 2-Methyl-5-nitroaniline was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. 2-Methyl-5-nitroaniline has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for 2-methyl-5-nitroaniline is 3.3×10^{-2} $(mg/kg/day)^{-1}$ for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for 2-methyl-5-nitroaniline is 1000.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR 2-METHYL-5-NITROANILINE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

EXECUTIVE SUMMARY

2-Methyl-5-nitroaniline is a crystalline yellow solid at room temperature (Weast, 1985). When heated to decomposition, this compound creates toxic fumes of nitrogen oxides and carbon monoxide (Sax, 1984; U.S. EPA, 1986a). 2-Methyl-5-nitroaniline is made by the nitration of o-toluidine with concentrated sulfuric acid (SDCAACC, 1971). Recent sources cite Pfister Chemical, Inc., as the only domestic manufacturer of this chemical (SRI, 1985; USITC, 1985). The U.S. EPA (1977) listed a total of seven manufacturers and importers in 1977 and prior years. During 1983, 44,226 pounds of this compound were imported through principal U.S. customs districts (USITC, 1984). 2-Methyl-5-nitroaniline is used as an intermediate in the synthesis of Pigment Red 17, Pigment Red 22 and a wide spectrum of azo dyes of various red, yellow, violet and brown hues (NCI, 1978).

If released to water, 2-methyl-5-nitroaniline should resist hydrolysis. The half-life for the reaction of 2-methyl-5-nitroaniline with alkyl peroxy radicals in water has been estimated to be 14 days. Experimental data indicate biodegradation of 2-methyl-5-nitroaniline under anaerobic conditions may occur. The potential exists for direct photolysis in water and the presence of algae may accelerate photochemical degradation. Adsorption to suspended solids and sediments by physical and chemical binding may be significant. Calculated BCFs indicate that bioaccumulation in aquatic organisms should not be significant.

If released to air, 2-methyl-5-nitroaniline vapor may react with photochemically generated hydroxyl radicals ($t_{1/2}$=7.99 hours, estimated). In addition, the potential exists for direct photolysis in the atmosphere. Oxidation by reaction with $O^3(P)$ atoms is not likely to be significant.

The compound may not transport long distances in the atmosphere because of its relatively short residence time in the atmosphere.

In moist soils, hydrolysis of 2-methyl-5-nitroaniline should not be a significant degradation process. An estimated K_{oc} of 1820 suggests that the compound has low mobility in soil. Mobility will be further decreased due to formation of covalent binding with humates in the soil. Volatilization from dry soil surfaces should also be insignificant. Information on the likely soil-catalyzed oxidation of this compound could not be located in the available literature as cited in the Appendix.

2-Methyl-5-nitroaniline has been detected in the effluent from 2,4,6-trinitrotoluene manufacturing (Spanggord et al., 1982) and has been identified as a volatile flavor component of baked potatoes (Coleman et al., 1980). The most probable route of dermal and inhalation exposure is by occupational exposure of workers involved in the production, use and handling of this compound.

Pertinent data regarding the absorption, distribution and excretion of 2-methyl-5-nitroaniline could not be located in the available literature as cited in the Appendix. In a study designed to investigate the metabolism of 2,4-dinitrotoluene, 2-methyl-5-nitroaniline, a metabolite of 2,4-dinitrotoluene, was reported to be reduced to 2,4-diaminotoluene by cecal microflora in rats (Mori et al., 1985).

NCI (1978) reported that 2-methyl-5-nitroaniline is carcinogenic in male and female B6C3F1 mice, but not in F344 rats of either sex. Dietary administration of 2-methyl-5-nitroaniline at 2300 ppm was associated with a significantly increased incidence of hepatocellular carcinomas in male and female mice. The appearance of hemangiosarcomas and hemangiomas in treated mice was not statistically significant, but was judged to be compound-

related since these tumors are rare in B6C3F1 mice. There were no statistically significant compound-related tumors in rats of either sex that were fed 2-methyl-5-nitroaniline at 50 or 100 ppm, but a dose-related increase in the incidence of hepatocellular carcinomas was observed in males. The only nonneoplastic effect was a reduction in growth observed in all rats and mice exposed to 2-methyl-5-nitroaniline (50 or 100 ppm, rats; 1200 or 2300 ppm, mice).

2-Methyl-5-nitroaniline was found to be mutagenic in Ames tests with Salmonella typhimurium (Spanggord et al., 1982; Dunkel et al., 1985). Data pertaining to the chronic toxicity, teratogenicity or reproductive effects of 2-methyl-5-nitroaniline could not be located in the available literature as cited in the Appendix. NIOSH (1986) reported an oral rat LD_{50} of 574 mg/kg for 2-methyl-5-nitroaniline.

A q_1^* of 3.3×10^{-2} $(mg/kg/day)^{-1}$ was derived from the incidences of hepatocellular carcinoma in female mice in the NCI (1978) bioassay. Water concentrations associated with increased lifetime risk at levels of 10^{-5}, 10^{-6} and 10^{-7} are 1.06×10^{-2}, 1.06×10^{-3} and 1.06×10^{-4} mg/ℓ. An F factor of 0.16 $(mg/kg/day)^{-1}$ was also derived from the incidence of hepatocellular carcinoma in female mice, placing 2-methyl-5-nitroaniline in Potency Group 3. Because human carcinogenicity data were lacking and evidence for carcinogenicity in animals was limited, 2-methyl-5-nitroaniline was classified as a U.S. EPA Group C Chemical, a possible human carcinogen. A Potency Group 3 and U.S. EPA Group C chemical has a LOW Hazard Ranking under CERCLA. An RQ of 1000 was derived, based on reduced growth rates in rats in the NCI (1978) study.

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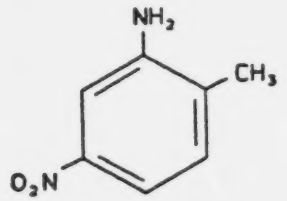
LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CS	Composite score
EC_{50}	Concentration effective to 50% of recipients (and all other subscripted concentration levels)
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dose levels)
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
TWA	Time-weighted average
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

2-Methyl-5-nitroaniline is also known as 5-nitro-O-toluidine, 2-amino-4-nitrotoluene and 2-methyl-5-nitrobenzeneamine. The dye industry commonly refers to this compound as Fast Scarlet Base G or Azoic Diazo Compound 12 (Color Index 37105) (NCI, 1978). The structure, CAS Registry number, empirical formula and molecular weight are as follows:



2-methyl-5-nitroaniline

Molecular weight: 152.16

Empirical formula: $C_7H_8N_2O_2$

CAS Registry number: 99-55-8

1.2. PHYSICAL AND CHEMICAL PROPERTIES

2-Methyl-5-nitroaniline is a crystalline yellow solid at room temperature (Weast, 1985). When heated to decomposition, this compound emits toxic fumes of nitrogen oxides and carbon monoxides (Sax, 1984; U.S. EPA, 1986a). 2-Methyl-5-nitroaniline is soluble in ethanol, ether and acetone (U.S. EPA, 1986a). Selected physical properties are as follows:

Melting point:	107°C	NCI, 1978
Boiling point:	378°C (estimated)	Neely and Blau, 1985
Vapor pressure at 20°C:	1.3×10^{-5} mm Hg (estimated)	Neely and Blau, 1985
Water solubility:	3708 mg/ℓ (estimated)	Lyman et al., 1982
Log K_{ow}:	1.96 (estimated)	U.S. EPA, 1986b
pK_a (at 25°C):	2.345	Robinson, 1967

The water solubility data was estimated from the log K_{ow} value and the equation log 1/S=0.996 log K_{ow}-0.339 (Lyman et al., 1982).

1.3. PRODUCTION DATA

2-Methyl-5-nitroaniline is produced by the nitration of o-toluidine with concentrated sulfuric acid (SDCAACC, 1971). Pfister Chemical, Inc., in Ridgefield, NJ, is the only reported domestic manufacturer of this compound (SRI, 1985; USITC, 1985). Table 1-1 lists companies that manufactured or imported this compound in 1977 and their corresponding import or production volumes (U.S. EPA, 1977).

During 1983, 44,226 pounds of 2-methyl-5-nitroaniline, listed as Color Index Azoic Diazo Component 12, base or as 5-nitro-O-toluidine, were imported through principal U.S. customs districts (USITC, 1984).

1.4. USES

2-Methyl-5-nitroaniline is used as an intermediate in the synthesis of Pigment Red (Color Index 12390) and Pigment Red 22 (Color Index 12315). When used in conjunction with certain Color Index coupling components, 2-methyl-5-nitroaniline also serves as an intermediate for a wide variety of azo dyes of various red, yellow, violet and brown hues (NCI, 1978).

1.5. SUMMARY

2-Methyl-5-nitroaniline is a crystalline yellow solid at room temperature (Weast, 1985). When heated to decomposition, this compound creates toxic fumes of nitrogen oxides and carbon monoxide (Sax, 1984; U.S. EPA, 1986a). 2-Methyl-5-nitroaniline is made by the nitration of o-toluidine with concentrated sulfuric acid (SDCAACC, 1971). Recent sources cite Pfister Chemical, Inc., as the only domestic manufacturer of this chemical (SRI, 1985; USITC, 1985). The U.S. EPA (1977) listed a total of seven manufacturers and importers in 1977 and prior years. During 1983, 44,226 pounds

TABLE 1-1

U.S. Manufacturers/Importers of 2-Methyl-5-nitroaniline[a]

Company	Manufacturer/ Importer	Production Volume (millions of pounds)
American Hoechst Corp.	importer	none[b]
Sandoz Color and Chem., NJ	importer	none[b]
Pfister Chem., Inc.	importer	0.010-0.100
Hilton-Davis Chem. Co.	manufacturer-site limited use	0.010-0.100
Blackman Uhler Chem. Div.	importer	0.010-0.100
Dianippon Ink and Chems. Amer., Inc.	importer	0.010-0.100
Cresent Chem. Co.	importer	small volume (confidential)

[a]Source: U.S. EPA, 1977

[b]These companies imported this chemical before 1977.

of this compound were imported through principal U.S. customs districts (USITC, 1984). 2-Methyl-5-nitroaniline is used as an intermediate in the synthesis of Pigment Red 17, Pigment Red 22 and a wide spectrum of azo dyes of various red, yellow, violet and brown hues (NCI, 1978).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Pertinent experimental data regarding the environmental fate of 2-methyl-5-nitroaniline could not be located in the available literature as cited in the Appendix. When possible, information regarding the fate and transport of this compound has been derived from its physical properties or its molecular structure.

2.1. WATER

2.1.1. Hydrolysis. Aromatic amines and aromatic nitro compounds are generally resistant to hydrolysis (Lyman et al., 1982). Based on its molecular structure, 2-methyl-5-nitroaniline should therefore be resistant to hydrolysis.

2.1.2. Oxidation. The rate constant for the reaction of 2-methyl-5-nitroaniline with alkyl peroxy radicals in water has been estimated to be 2×10^{-6} M^{-1} $hour^{-1}$ based on functional group reactivity with the alkyl peroxy radicals (Jaber et al., 1984). Assuming an ambient hydroxyl radical concentration of 10^{-9} M (Mill et al., 1980), the alkyl peroxy reaction half-life has been calculated to be ~14 days. In general, the reaction of a compound with singlet oxygen in water is less rapid than the alkyl peroxy reaction.

2.1.3. Biodegradation. The 2-methyl-5-nitroaniline that formed during anaerobic biodegradation of 2,4-dinitrotoluene by a mixed bacterial population derived from activated sludge had an apparently short half-life ($t_{1/2}$<10 days) (Liu et al., 1984). No information on the biodegradability of the compound under aerobic conditions was available in the literature as cited in the Appendix.

2.1.4. Photolysis. 2-Methyl-5-nitroaniline in methanol absorbs light in the environmentally significant range of wavelenths >290 nm (Sadtler, n.d.), suggesting that the potential exists for the direct photolysis of 2-methyl-5-nitroaniline in water. This photoreactivity may be further accelerated by algae present in natural water as observed by Zepp and Schlotzhauer (1983) with anilines and substituted anilines.

2.1.5. Transport Processes.

2.1.5.1. **ADSORPTION** -- Based on the estimated K_{oc} of 1820 for 2-methyl-5-nitroaniline (Section 2.3.2.), physical adsorption of this compound to suspended solids and sediments may be significant. Experimental data indicate that primary aromatic amines form covalent bonds with humates present in natural waters (Parris, 1980). The result of this irreversible binding process is that lesser amounts of the free compound are made available in the aquatic phase for further chemical, physical and microbial processes that would lead to the loss of the chemical.

2.1.5.2. **BIOACCUMULATION** -- The BCF for 2-methyl-5-nitroaniline can be calculated using the following equations (Lyman et al., 1982):

$$\text{Log BCF} = 0.76 \log K_{ow} - 0.23 \qquad (2\text{-}1)$$

$$\text{Log BCF} = 1.119 \log K_{oc} - 1.579 \qquad (2\text{-}2)$$

Based on an estimated log K_{ow} of 1.96 (U.S. EPA, 1986b) and log K_{oc} of 3.26, the BCF for 2-methyl-5-nitroaniline has been calculated to be 18 and 117, respectively. These BCF values indicate that bioconcentration in aquatic organisms should not be significant.

2.2. AIR

2.2.1. Oxidation. The rate constant for the reaction of 2-methyl-5-nitroaniline with photochemically generated hydroxyl radicals has been estimated to be 3.01×10^{-11} cm^3/molecule-sec at 25°C (U.S. EPA, 1986c).

Assuming an ambient hydroxyl radical concentration of 8.0×10^5 molecules/cm^3, the reaction half-life has been calculated to be 7.99 hours. 2-Methyl-5-nitroaniline is not likely to react with $O^3(P)$ atoms in the atmosphere (U.S. EPA, 1986c).

2.2.2. Photolysis. The absorption of UV light of wavelengths >290 nm by 2-methyl-5-nitroaniline (see Section 2.1.3.) suggests that direct photolysis is a potential degradation mechanism.

2.2.3. Physical Transport. Considering that the calculated vapor pressure for 2-methyl-5-nitroaniline of 1.3×10^{-5} mm Hg at 20°C, the compound is expected to be partly in the vapor phase and partly adsorbed onto airborne particulate matter (Eisenreich et al., 1981). Both wet and dry deposition will remove some of the compound from the atmosphere, but reaction with HO radical is expected to be the dominating removal mechanism. If the chemical has a short residence time (~12 hours) in the atmosphere, it may not transport long distances in the atmosphere.

2.3. SOIL

2.3.1. Hydrolysis. Based on the molecular structure of 2-methyl-5-nitroaniline, hydrolysis in moist soil should not be a significant degradation process (see Section 2.2.1.).

2.3.2. Adsorption. Using the molecular topology and quantitative structure-activity relationship of Sabljic (1984), the K_{oc} of 2-methyl-5-nitroaniline has been estimated to be 1820, a value which suggests that the compound may have low mobility in soil (Swann et al., 1983). The formation of covalent bonds with humates may further lower the mobility in soil.

2.3.3. Volatilization. Considering the relatively low vapor pressure of 2-methyl-5-nitroaniline (1.3×10^{-5} mm Hg at 20°C, estimated), volatilization from dry soil surfaces should be insignificant.

2.4. SUMMARY

If released to water, 2-methyl-5-nitroaniline should resist hydrolysis. The half-life for the reaction of 2-methyl-5-nitroaniline with alkyl peroxy radicals in water has been estimated to be 14 days. Experimental data indicate biodegradation of 2-methyl-5-nitroaniline under anaerobic conditions may occur. The potential exists for direct photolysis in water and the presence of algae may accelerate photochemical degradation. Adsorption to suspended solids and sediments by physical and chemical binding may be significant. Calculated BCFs indicate that bioaccumulation in aquatic organisms should not be significant.

If released to air, 2-methyl-5-nitroaniline vapor may react with photochemically generated hydroxyl radicals ($t_{1/2}$=7.99 hours, estimated). In addition, the potential exists for direct photolysis in the atmosphere. Oxidation by reaction with $O^3(P)$ atoms is not likely to be significant. The compound may not transport long distances in the atmosphere because of its relatively short residence time in the atmosphere.

In moist soils, hydrolysis of 2-methyl-5-nitroaniline should not be a significant degradation process. An estimated K_{oc} of 1820 suggests that the compound has low mobility in soil. The mobility will be further decreased by the formation of covalent bonds with humates in the soil. Volatilization from dry soil surfaces should also be insignificant. No information on the likely soil-catalyzed oxidation of this compound was available in the literature as cited in the Appendix.

3. EXPOSURE

3.1. WATER

2-Methyl-5-nitroaniline has been detected at levels ranging from 0.002-0.10 mg/ℓ in the wastewater from the manufacture of 2,4,6-trinitrotoluene (Spanggord et al., 1982b).

3.2. INHALATION

Pertinent data regarding the monitoring of 2-methyl-5-nitroaniline in the atmosphere could not be located in the available literature as cited in the Appendix. The most probable route of inhalation exposure is by occupational exposure of workers involved in the production, use and handling of this compound.

3.3. FOOD

2-methyl-5-nitroaniline has been identified by mass spectrometry as a volatile flavor component of Idaho Russet Burbank baked potatoes (Coleman et al., 1980).

3.4. DERMAL

Pertinent data regarding the monitoring of dermal exposure to 2-methyl-5-nitroaniline could not be located in the available literature as cited in the Appendix. The most probable route of skin exposure is by occupational exposure of workers involved in the production, use and handling of this compound.

3.5. SUMMARY

2-Methyl-5-nitroaniline has been detected in the effluent from 2,4,6-trinitrotoluene manufacturing (Spanggord et al., 1982a) and has been identified as a volatile flavor component of baked potatoes (Coleman et al., 1980). The most probable route of dermal and inhalation exposure is by occupational exposure of workers involved in the production, use and handling of this compound.

4. PHARMACOKINETICS

Pertinent data regarding the absorption, distribution and excretion of 2-methyl-5-nitroaniline could not be located in the available literature as cited in the Appendix. In a study designed to investigate the metabolism of 2,4-dinitrotoluene, 2-methyl-5-nitroaniline, a metabolite of 2,4-dinitrotoluene, was reported to be reduced to 2,4-diaminotoluene by fecal microflora in rats (Mori et al., 1985).

5. EFFECTS

5.1. CARCINOGENICITY

The carcinogenic potential of 2-methyl-5-nitroaniline (5-nitrotoluidine) was tested in a bioassay in B6C3F1 mice and F344 rats (NCI, 1978). Groups of 50 male and 50 female rats were fed TWA concentrations of 0.005 or 0.01% (50 or 100 ppm) 2-methyl-5-nitroaniline in the diet for 78 weeks. Males and low-dose females were maintained for an additional 30 weeks, then killed and necropsied. High-dose females were killed after 31 weeks posttreatment. A group of 50 male and 50 female controls were maintained for 108 weeks. Groups of 50 male and 50 female mice were fed TWA concentrations of 0.12 or 0.23% (1200 or 2300 ppm) for 78 weeks, then killed and necropsied after an additional 19 weeks (males and low-dose females) or 20 weeks (high-dose females). A group of 50 male and 50 female control mice was maintained for 95-96 weeks. The treatment protocols for rats and mice are summarized in Table 5-1.

There were no compound-related effects on survival in either rats or mice. Reductions in growth in comparison with controls were observed in high-dose male rats, low- and high-dose female rats and all treated mice. These reductions were more severe among females. There were no significant compound-related nonneoplastic lesions in rats or mice.

A dose-related ($p<0.001$, Cochran-Armitage test) increase in the incidence of hepatocellular carcinoma was observed in male and female mice. No hepatic tumors were considered to be benign. Incidences were significantly different from controls ($p<0.001$, Fisher Exact test) only among high-dose mice (Table 5-2). Hemangiosarcomas (male and female) and hemangiomas (males only) were observed in treated mice. Although incidences of these

TABLE 5-1

Treatment Protocol for Rats and Mice*

Species	TWA Concentration (%)	Exposure (%)	Duration (weeks)
Rat	0.005	0.0045	8
		0.005	70
		0	30
	0.01	0.009	8
		0.01	70
		0	30 (males)
			31 (females)
Mouse	0.12	0.005	18
		0.15	60
		0	19
	0.23	0.01	18
		0.30	60
		0	19 (males)
			20 (females)

*Source: NCI, 1978

TABLE 5-2

Incidence of Tumors in B6C3F1 Mice Fed 2-Methyl-5-Nitroaniline for 78 Weeks[a]

Sex	Dose (ppm)	Duration of Study (weeks)	Tumor Type	Tumor Incidence (p value)
F	0	96	hepatocellular	2/47 (p>0.001)[b]
	1200	97	carcinoma	7/46 (NS) (p>0.05)[c]
	2300	98		20/45 (p<0.001)[c]
	0	96	hemangiosarcoma	1/48 (NS) (p>0.05)[b]
	1200	97		5/47 (NS) (p>0.05)[c]
	2300	98		3/47 (NS) (p>0.05)[c]
M	0	95	hepatocellular	12/50 (p<0.001)[b]
	1200	97	carcinoma	12/44 (NS) (p>0.05)[c]
	2300	97		29/45 (p<0.001)[c]
	0	95	hemangiosarcoma	1/50 (NS) (p>0.05)[b]
	1200	97	or hemangioma	0/47 (NS) (p>0.05)[c]
	2300	97		4/48 (NS) (p>0.05)[c]

QUALITY OF EVIDENCE

Strengths of Study: The compound was administered to both sexes at two dose levels. Adequate number of animals per group; natural route of exposure; adequate duration of exposure.

Weakness of Study: Purity of compound not reported.

Overall Adequacy: Adequate

[a]Source: NCI, 1978

[b]Cochran-Armitage Test

[c]Fisher exact test

NS = Not significant

tumors in treated mice were not significantly different from controls, the tumors were considered to be compound-related since they rarely occur in B6C3F1 mice.

There were no compound-related significantly increased incidences of tumors of any type in F344 rats. There was a significant dose-related increase ($p=0.039$, Cochran-Armitage test) in the incidence of hepatocellular carcinoma in male rats, but the incidences in either low- or high-dose rats were not significantly different from controls ($p>0.05$, Fisher Exact test). On the basis of these results, NCI (1978) concluded that 2-methyl-5-nitroaniline is carcinogenic to male and female B6C3F1 mice but not F344 rats.

No other studies pertaining to the carcinogenicity of 2-methyl-5-nitroaniline were located in the available literature as cited in the Appendix.

5.2. MUTAGENICITY

Dunkel et al. (1985) reported on the NCI/NTP testing of 63 chemicals in a collaborative program in which four laboratories participated. Salmonella strains TA98, TA100, TA1535, TA1537 and TA1538 as well as E. coli WP2 uvrA were employed. All chemicals were tested without metabolic activation and with liver S-9 preparations from uninduced and Aroclor 1254-induced F344 rats, B6C3F1 mice and Syrian hamsters. In all tests 2-methyl-5-nitroaniline was tested at half-log intervals from 3.3-3333.3 µg/plate. Results clearly indicate that 2-methyl-5-nitroaniline was mutagenic both without and with essentially all activation systems employed in TA98, TA100, TA1537 and TA1538. All laboratories reported negative results in E. coli and three of the four laboratories reported negative results in TA1535 with toxicity apparent at the highest concentration, with one laboratory reporting positive results in TA1535.

Spanggord et al. (1982b) reported similar findings in their testing of 2-methyl-5-nitroaniline in Salmonella using liver S-9 preparations from Aroclor 1254-induced Sprague-Dawley rats as the source of exogenous activations. The only condition under which negative results were observed was in strain TA1535 with S-9 activation.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of 2-methyl-5-nitroaniline could not be located in the available literature as cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

Data pertaining to the other reproductive effects of 2-methyl-5-nitroaniline could not be located in the available literature as cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

NCI (1978) is the only chronic study conducted with 2-methyl-5-nitroaniline (see Section 5.1.). The only nonneoplastic effect observed was growth reduction in male and female F344 rats and B6C3F1 mice. Average weights were ~0.40 kg for control and low-dose male rats and ~0.35 kg for low- and high-dose female rats; ~0.22 kg for control female rats and ~0.19 kg for low- and high-dose female rats; 0.036 kg for control and 0.030 kg for low- and high-dose male mice; and 0.034 kg for control and 0.025 kg for low- and high-dose female mice.

5.6. OTHER RELEVANT INFORMATION

NIOSH (1986) reported an oral rat LD_{50} of 574 mg/kg for 2-methyl-5-nitroaniline.

5.7. SUMMARY

NCI (1978) reported that 2-methyl-5-nitroaniline is carcinogenic in male and female B6C3F1 mice, but not in F344 rats of either sex. Dietary administration of 2-methyl-5-nitroaniline at 2300 ppm was associated with a

significantly increased incidence of hepatocellular carcinomas in male and female mice. The appearance of hemangiosarcomas and hemangiomas in treated mice was not statistically significant, but was judged to be compound-related since these tumors are rare in B6C3F1 mice. There were no statistically significant compound-related tumors in rats of either sex that were fed 2-methyl-5-nitroaniline at 50 or 100 ppm, but a dose-related increase in the incidence of hepatocellular carcinomas was observed in males. The only nonneoplastic effect was a reduction in growth observed in all rats and mice exposed to 2-methyl-5-nitroaniline (50 or 100 ppm, rats; 1200 or 2300 ppm, mice).

2-Methyl-5-nitroaniline was found to be mutagenic in Ames tests with Salmonella typhimurium (Spanggord et al., 1982b; Dunkel et al., 1985). Data pertaining to the chronic toxicity, teratogenicity or reproductive effects of 2-methyl-5-nitroaniline could not be located in the available literature as cited in the Appendix. NIOSH (1986) reported an oral rat LD_{50} of 574 mg/kg for 2-methyl-5-nitroaniline.

6. AQUATIC TOXICITY

6.1. ACUTE

Liu et al. (1983) and Pearson et al. (1979) reported 96-hour LC_{50} values for 2-methyl-5-nitroaniline of 68.8 and 71.3 mg/ℓ, respectively, in fathead minnows, Pimephales promelas. These authors also reported 48-hour EC_{50} values for immobilization of Daphnia magna of 22.4 and 22.5 mg/ℓ, respectively.

6.2. CHRONIC

Pertinent data regarding the chronic toxicity of 2-methyl-5-nitroaniline to aquatic organisms could not be located in the available literature as cited in the Appendix.

6.3. PLANTS

Pertinent data regarding the effect of 2-methyl-5-nitroaniline on aquatic plants could not be located in the available literature as cited in the Appendix.

6.4. RESIDUES

Liu et al. (1983) calculated a BCF of 5.93 for 2-methyl-5-nitroaniline in aquatic organisms. This value was based on physical and chemical properties rather than on experimental data.

6.5. SUMMARY

Fathead minnow 96-hour LC_{50} values of 68.8 and 71.3 mg/ℓ have been reported. EC_{50} values for immobilization of Daphnia magna were 22.4 and 22.5 mg/ℓ (Liu et al., 1983; Pearson et al., 1979). Liu et al. (1983) calculated a BCF of 5.93 for 2-methyl-5-nitroaniline in aquatic organisms.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Pertinent guidelines and standards, including EPA ambient water and air quality criteria, drinking water standards, FAO/WHO ADIs, EPA or FDA tolerances for raw agricultural commodities or foods and ACGIH, NIOSH or OSHA occupational exposure limits could not be located in the available literature as cited in the Appendix.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic biota from the effects of 2-methyl-5-nitroaniline could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

NCI (1978) reported that 2-methyl-5-nitroaniline is carcinogenic in male and female B6C3F1 mice, but not in F344 rats of either sex. Dietary administration of 2-methyl-5-nitroaniline (0.23%) was associated with a significantly increased incidence of hepatocellular carcinomas in male and female mice. The appearance of hemangiosarcomas and hemangiomas in treated mice was not statistically significant, but was judged to be compound-related since these tumors are rare in B6C3F1 mice. There were no statistically significant, compound-related tumors in rats of either sex that were fed 2-methyl-5-nitroaniline at 50 or 100 ppm, but a dose-related increase in the incidence of hepatocellular carcinomas was observed in males. The only nonneoplastic effect was a reduction in growth observed in all rats and mice exposed to 2-methyl-5-nitroaniline (50 or 100 ppm, rats; 1200 or 2300 ppm, mice).

2-Methyl-5-nitroaniline was found to be mutagenic in Ames tests with Salmonella typhimurium (Spanggord et al., 1982b; Dunkel et al., 1985). Data pertaining to the chronic toxicity, teratogenicity or reproductive effects of 2-methyl-5-nitroaniline could not be located in the available literature as cited in the Appendix. NIOSH (1986) reported an oral rat LD_{50} of 574 mg/kg for 2-methyl-5-nitroaniline.

According to U.S. EPA criteria (U.S. EPA, 1986d), there is limited evidence that 2-methyl-5-nitroaniline is carcinogenic to animals; therefore, it is appropriate to calculate a q_1^*. The data used to calculate the q_1^*s for the incidences of hepatocellular carcinoma in female and male mice in the NCI (1978) study are presented in Tables 8-1 and 8-2, respectively. The transformed doses were calculated by multiplying the dietary

TABLE 8-1

Cancer Data Sheet for Derivation of a q_1^*

Compound: 2-methyl-5-nitroaniline

Reference: NCI, 1978

Species, strain, sex: mouse, B6C3F1, female

Route, vehicle: oral, diet

Length of Exposure (le) = 78 weeks

Length of Experiment (LE) = 98 weeks (high dose), 97 weeks (low dose)

Lifespan of Animal (L) = 104 weeks

Body weight = 0.025 kg (measured)

Tumor type and site: hepatocellular carcinoma

Exposure (ppm)	Transformed Dose (mg/kg/day)†	Incidence No. Responding/No. Tested
0	0	2/47
1200	125	7/46
2300	238	20/45

†Dose = ppm x 0.13xle/LE

Unadjusted q_1^* from study = 1.939559×10^{-3} $(mg/kg/day)^{-1}$

Human $q_1^* = 3.3 \times 10^{-2}$ $(mg/kg/day)^{-1}$

TABLE 8-2

Cancer Data Sheet for Derivation of q_1^*

Compound: 2-methyl-5-nitroaniline

Reference: NCI, 1978

Species, strain, sex: mouse, B6C3F1, male

Route, vehicle: oral, diet

Length of Exposure (le) = 78 weeks

Length of Experiment (LE) = 97 weeks

Lifespan of Animal (L) = 104 weeks

Body weight = 0.025 kg (measured)

Tumor site and type: hepatocellular carcinoma

Exposure (ppm)	Transformed Dose (mg/kg/day)†	Incidence No. Responding/No. Tested
0	0	12/50
1200	125	12/44
2300	240	29/45

†Dose = ppm x 0.13xle/Le

Unadjusted q_1^* from study = 1.878033×10^{-3} $(mg/kg/day)^{-1}$

Human $q_1^* = 3.1 \times 10^{-2}$ $(mg/kg/day)^{-1}$

concentrations by a food factor of 0.13 (it is assumed that a mouse consumes a daily amount of food equal to 13% of its body weight) and by the length of exposure divided by the length of the study. The unadjusted q_1^*s were calculated using the computerized multistage model (Howe and Crump, 1982). The human q_1^*s were calculated by multiplying the unadjusted q_1^*s by the cube root of the ratio of the reference human body weight (70kg) to the mouse body weights (0.025 kg, females; 0.03 kg, males) and by the cube of the ratio of the mouse lifespan (104 weeks) to the duration of the study (97.5 weeks). As seen from Tables 8-1 and 8-2, a slightly higher q_1^* of 3.3×10^{-2} $(mg/kg/day)^{-1}$ resulted from the data for females. The concentrations in water associated with increased lifetime risk at levels of 10^{-5}, 10^{-6} and 10^{-7} are 1.06×10^{-2}, 1.06×10^{-3} and 1.06×10^{-4} mg/ℓ, assuming that a 70 kg human consumes 2 ℓ water/day.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Studies designed to investigate the chronic toxicity of 2-methyl-5-nitroaniline could not be located in the available literature as cited in the Appendix. As summarized in Table 9-1, the only nonneoplastic effect observed in the cancer bioassay on 2-methyl-5-nitroaniline (NCI, 1978) was a slight reduction in growth in B6C3F1 mice and F344 rats (see Sections 5.1. and 5.5.).

The highest CS, a value of 13.7, can be derived on the basis of decreased growth in female F344 rats fed 50 ppm 2-methyl-5-nitroaniline in the diet for 78 weeks (NCI, 1978). A food factor of 0.05 is used to convert the dietary concentration to a dose of 2.5 mg/kg/day. A human MED of 24.4 mg/day is derived by multiplying 2.5 mg/kg/day by the product of the cube root of the ratio of rat weight (0.19 kg) to human weight (70 kg). The MED corresponds to an RV_d of 3.4. An RV_e of 4 is assigned on the basis of decreased growth. Multiplying the RV_d by the RV_e yields a CS of 13.7. This is equivalent to an RQ of 1000. These data are summarized in Tables 9-2 and 9-3.

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Dietary administration of 2-methyl-5-nitroaniline was associated with a significantly increased incidence of hepatocellular carcinomas in male and female B6C3F1 mice (NCI, 1978). The appearance of hemangiosarcomas and hemangiomas in treated mice was not statistically significant, but was judged to be compound-related since these tumors are rare in B6C3F1 mice. There were no statistically significant compound-related tumors in F344 rats of either sex fed 2-methyl-5-nitroaniline (NCI, 1978), but a dose-related increase in the incidence of hepatocellular carcinomas was observed in males (see Section 5.1. and Table 5-2).

TABLE 9-1

Oral Toxicity Summary for 2-Methyl-5-Nitroaniline Administered in the Diet[a,b]

Species/Strain	Sex	No. at Start	Average Weight[c] (kg)	Exposure for 78 Weeks (ppm)	Transformed Animal Dose (mg/kg/day)[d]	Response
Rat/F344	M	50	0.35	100	5.0	decreased growth
Rat/F344	F	50	0.19	50	2.5	decreased growth
Rat/F344	F	50	0.19	100	5.0	decreased growth
Mouse/B6C3F1	M	50	0.03	1200	156	decreased growth
Mouse/B6C3F1	M	50	0.03	2300	299	decreased growth
Mouse/B6C3F1	F	50	0.025	1200	156	decreased growth
Mouse/B6C3F1	F	50	0.025	2300	299	decreased growth

[a]Source: NCI, 1978

[b]Purity not reported

[c]Average weights for controls were 0.40 kg (male rats); 0.30 (female rats), 0.36 (male mice) and 0.034 (female mice)

[d]Food factors of 0.05 and 0.13 were assumed for rats and mice, respectively, in the conversion of ppm to mg/kg/day.

NR = Not reported

TABLE 9-2

Oral Composite Scores for 2-Methyl-5-Nitroaniline*

Species	Animal Dose (mg/kg/day)	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ
Rat (F)	2.5	24.4	3.4	Decreased growth	4	13.7	1000

*Source: NCI, 1978

TABLE 9-3

2-Methyl-5-Nitroaniline

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	24.4 mg/day
Effect:	decreased growth
Reference:	NCI, 1978
RV_d:	3.4
RV_e:	4
Composite Score:	13.7
RQ:	1000

*Equivalent human dose

According to U.S. EPA criteria, there is limited evidence that 2-methyl-5-nitroaniline is carcinogenic to animals because there was a definitive malignant tumor response in a single well-conducted experiment (U.S. EPA, 1986d). There are no data that can be used to assess the carcinogenic potential of the compound in humans. 2-Methyl-5-nitroaniline is, therefore, best classified as a U.S. EPA Group C chemical, a possible human carcinogen (U.S. EPA, 1986d). An F factor of 0.16 $(mg/kg/day)^{-1}$ can be derived on the basis of the incidence of hepatocellular carcinomas in female B6C3F1 mice (NCI, 1978). Data used in the estimation of the potency factor are summarized in Table 9-4.

A potency factor of <1 places this chemical in Potency Group 3 and, combined with a U.S. EPA Group C classification, puts 2-methyl-5-nitroaniline in the LOW category of the CERCLA Hazard Ranking scheme.

TABLE 9-4

Derivation of Potency Factor (F) for 2-Methyl-5-Nitroaniline

Reference:	NCI, 1978		
Exposure route:	oral		
Species:	mouse		
Strain:	B6C3F1		
Sex:	female		
Vehicle or physical state:	diet		
Body Weight:	0.025 kg		
Duration of treatment:	78 weeks		
Duration of study:	98 weeks (high dose), 97 weeks (low dose)		
Lifespan of animal:	104 weeks		
Target organ:	liver		
Tumor type:	hepatocellular carcinoma		
Experimental doses/exposure (ppm):	0	1200	2300
Transformed doses[a] (mg/kg/day):	0	125.4	237.9
Tumor incidence:	12/48	17/47	24/47
Unadjusted $1/ED_{10}$:	9.3823593×10^{-3} (mg/kg/day)$^{-1}$		
Adjusted $1/ED_{10}$ (F factor)[b]:	1.60×10^{-1} (mg/kg/day)$^{-1}$		

[a]Dose = ppm x 0.13 x 1e/LE where 0.13 = food factor, 1e = duration of treatment, LE = duration of study

[b]Adjusted $1/ED_{10}$ = unadjusted $1/ED_{10}$ x $(70/0.025)^{1/3}$ x $(104/97.5)^3$

10. REFERENCES

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U.S. EPA. 1986c. Graphical Exposure Modeling System (GEMS) fate of atmospheric pollutants (FAP) data base. Office of Toxic Substances, U.S. EPA, Washington, DC.

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USTIC (U.S. International Trade Commission). 1985. Synthetic Organic Chemicals. United States Production and Sales, 1984. Washington, DC.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

GLOBAL
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in April, 1986. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985-1986. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1985-1986. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

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Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

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